REMARKS

I. Status of the Claims

Claims 245, 247-255, 262, 265 and 268-271 were pending with the October 4, 2010 Office Action. Claims 268 and 269 are withdrawn and claims 245, 247-255, 262, 265, 270 and 271 were examined in the Office Action. With this response, claims 245, 249-255, 262, 270 and 271 are amended. The claim amendments are made without prejudice or disclaimer and provide no new matter. Support of the claim amendments is found at least at paragraphs **[0254]**, **[0262]** and **[0269]** of the specification as published in US Publication 2003/0104620. Applicants note that the amendment in claims 245, 262, 270, and 271 replacing "nucleic acid sequence" with "nucleotide sequence" is made solely to avoid using "nucleic acid" in two different contexts, since "nucleic acid" is already used in the phrase "nucleic acid construct". Claims 245, 247-255, 262, 265 and 270-271 are presented for reconsideration.

II. Rejection under 35 U.S.C. § 112, First Paragraph – Enablement

Claims 245, 247-255, 262, 265, 270 and 271 are rejected under 35 U.S.C. 112, first paragraph, enablement requirement. The Office Action asserts at p. 3 that "...there is not sufficient description for choosing the location of insertion of the intron sequences within the context of the instant invention, as it is not evident that insertion of any intron into any sequence encoding any intron, especially wherein the insertion is at any position, would result in the instantly recited outcomes. The instant claims are not closed to introns with any specific structural characteristic that would narrow the genus to those introns with any specific structural characteristic that would narrow the genus to those introns that are predictably spliced in eukaryotes." Applicants respectfully request reconsideration and withdrawal of this rejection in light of the following discussion.

Applicants assert that the description in the instant specification, with the known prior art at the time of filing, was sufficient to allow the skilled artisan to practice the invention for its full scope. As discussed in the Office Action at p. 4, at the time of filing

there were several examples (Schwartz et al., Mayeda et al., and Gatermann et al.) of artificial introns being inserted into genes, where the introns were correctly spliced during processing as predicted. The instant specification adds Example 19. Although the Office Action points to Balvay et al. that occasionally a secondary structure can lead to unpredictability, nevertheless, the skilled artisan could design a multitude of the claimed constructs using the teachings of the instant specification and prior art, where a non-native intron is inserted into a gene where it would likely be properly and predictably excised during processing.

The Office Action also points to Jaillon et al. as teaching that "...short introns recognized by the intron definition mechanism cannot be efficiently predicted solely on the basis of sequence motifs." In this regard, Applicants assert that such a teaching actually provides valuable prior art guidance to the skilled artisan practicing the instant invention in designing non-native introns by teaching that certain intron structures are less predictable than other intron structures, for example as utilized by Schwartz et al., Mayeda et al., Gatermann et al., and the Applicants in Example 19.

Applicants additionally assert that the claims, while possibly encompassing some inoperative embodiments, are nonetheless enabled, since "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. **The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art.** Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)" MPEP 2164.08(b) (emphasis added). Thus, the claims need not provide specific intron structures and insertion sites etc. since the skilled artisan, by making use of the prior art teachings, e.g., Schwartz et al., Mayeda et al., Gatermann et al., Balvay et al. and Jaillon et al., as well as the structures of the tens of thousands of introns and surrounding sequences identified in the prior art, could design thousands of different non-native intron structures for insertion into multiple sites of thousands of different genes that would likely be properly excised during processing. Further, any

particular non-native intron inserted into any particular site in any particular gene could be tested to determine whether that combination is properly processed without undue experimentation. This is all that is required for enablement for the instant claims.

In view of the above discussion, Applicants assert that the claims are enabled for their full scope. Withdrawal of the enablement rejection under 35 U.S.C. 112, first paragraph, is therefore respectfully requested.

III. Double Patenting Rejections

Claims 245, 247-255, 262, 265, 270 and 271 are provisionally rejected on the ground of obviousness-type double patenting (ODP) as being unpatentable over claims 1 and 2 of copending Application No. 11/929,055. Since these rejections are dependent on the scope of the final claims in both the instant application and application 11/929,055, Applicants will provide a terminal disclaimer where necessary when a proper ODP rejection is the only rejection remaining in this application.

IV. Rejections under 35 U.S.C. § 102

Claims 255 and 265 are rejected under 32 U.S.C. 102(b) as anticipated by Schwartz et al. (1993, Gene 127:233-236). Applicants request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The Office Action asserts that "Schwartz et al. teaches introduction of an intron from a hamster gene into a neo gene such that splicing of the neo gene mRNA results in the synthesis of active aminoglycoside phosphotransferase. The unspliced construct is inactive in E. coli, but confers resistance to G418 when tran[s]fected into mouse and hamster cells." By contrast, claim 255 recites:

> A nucleic acid construct which comprises a sequence that encodes a gene product, said construct further comprising an intron sequence non-native to said gene product, wherein (a) said intron sequence is within the sequence encoding said gene product; (b) said gene product is incapable of being expressed in a prokaryotic cell due to a stop codon and/or a frameshift mutation introduced by the presence of said intron; and (c) said gene product would be lethal specifically

> to a prokaryotic cell in the absence of said non-native intron, which when in a eukaryotic cell, said intron is removed during processing and wherein said gene product is expressed in a eukaryotic cell after removal of said intron.

In the response dated July 26, 2010, Applicants argued that Schwartz et al. do not teach "(c) said gene product would be lethal ["toxic" before the current amendments] specifically to a prokaryotic cell in the absence of said non-native intron". The Action responds that

> [I]t is noted that the instant specification does not define the term 'toxic' (now 'lethal'). The broadest reasonable interpretation of toxic includes being harmful. Since the bacteria containing the intron were unable to grow, while those not containing the intron were able to grow, lack of the intron is harmful or 'toxic' to the growth.

However, this assertion does not make sense. If "those not containing the intron were able to grow," as in the above quote, then lack of the intron cannot be harmful or toxic to growth. Further, these assertions are inconsistent with the teachings of Schwartz et al. In Schwartz et al., lack of the intron is not harmful to growth but rather allows growth, indicating that the *neo* gene product is not toxic. The Schwartz et al. construct encodes an aminoglycoside phosphotransferase (AGPT) (the *neo* gene product), encoding G418 resistance. The intron prevents expression of the active enzyme in *E. coli*. If the gene were expressed in *E. coli* without the intron, then the *E. coli* would be resistant to G418 and could grow. Thus, the intron prevents the bacteria from growing in the presence of G418, and the gene product is not lethal to the prokaryotic cell without the intron. Thus, in Schwartz et al., the absence of the intron allows the *E. coli* to express the enzyme and grow in the presence of G418. Thus, contrary to claim element (c), the gene product is not "toxic" to a prokaryotic cell in the absence of the non-native intron.

Further to this claim element, Applicants assert that the specification does discuss "lethal" at least at paragraph **[0269]** of the specification as published as US 2003/0104620, as gene products that actively kill the cells, for example as "enzymes which destroy bacterial cell walls." An AGPT gene, as utilized in Schwartz, which

prevents death of prokaryotes in the presence of G418, could thus not conceivably be considered a lethal gene product.

Aside from Schwartz et al. not teaching a lethal gene product, Schwartz et al. do not teach the removal of a non-native intron providing a "gene product [that] is expressed in a eukaryotic cell without any change in amino acid sequence from the native gene" since Schwartz et al. teaches that the intron-containing AGPT gene ("*neo*"), when correctly spliced, "would encode seven additional aa compared to *neo* mRNA." Schwartz et al., page 234.

Based on the above discussion, it is clear that Schwartz et al. do not teach or suggest every element of claims 255 (and dependent claim 265), and thus do not anticipate those claims. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. 102(e).

V. Rejections under 3 5 U.S.C. § 103

Claims 245, 257-255, 262, 265, 270 and 271 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz et al. (described under **IV.** above) in view of Mount (1982, Nucleic Acids Research 10: 459-472) and Deuschle et al. (1989, Proc. Natl. Acad. Sci. USA 86:5400-5404). The Office Action asserts, at p. 11, that Schwartz et al. teach all elements of the claims except that "Schwartz et al. do not teach the system specific to a polymerase, do not teach (C/A)AG sites." Mount is cited for teaching "splice junction sequences such as (C/A)AG and teach that the sequences have a possible role as signals for processing" and Deuschle et al. is cited for teaching "that a specific transcription activity can be regulated over a range of several orders of magnitude in higher eukaryotic cells." (both quotes from p. 11 of Office Action). Applicants respectfully request reconsideration and withdrawal of this rejection in light of the following comments.

With respect to claim 245 and 270, Applicants disagree with the assertion in the Office Action on p. 12 that "[i]t would have been obvious to insert the intron into a sequence encoding a polymerase given that it was known in the art that bacteriophage

T3 RNA polymerases are crucial in gene expression systems that regulate genes in eukaryotic cells. One would have been motivated to do so in order to attempt to control the expression of the polymerase in prokaryotic/eukaryotic cells since Shwartz et al. teaches that introns can be inserted to control differential expression." The rationale that a polymerase is crucial in gene expression systems that regulate genes in eukaryotic cells is not a reason for preventing expression of the polymerase in prokaryotes, since prokaryotes would ostensibly be unaffected by expression of a polymerase that regulates genes in eukaryotes. Further, since the Office Action provides no other source for the idea that a nucleic acid construct could usefully confer expression of a polymerase in eukaryotes but not prokaryotes, that idea was clearly taken from the instant specification, and is thus impermissible hindsight.

By contrast, the instant specification, at least at paragraph **[0275]** of the specification as published as US 2003/0104620, provides a rationale for having a polymerase expressed in eukaryotes but not prokaryotes – to express a gene toxic or lethal to prokaryotes but not eukaryotes where the gene is controlled by a promoter of the polymerase. An additional rationale is provided at paragraph **[0254]** of US 2003/0104620 and implicit in claim 245 – the use of a nucleic acid construct comprising an encoded polymerase and a recognition site of the polymerase to produce multiple copies of a transcriptional unit, e.g., encoding a prokaryotic toxin, in a eukaryotic cell. Thus, the expression of a polymerase in a eukaryote but not a prokaryote utilizing the claimed constructs is not obvious.

With respect to claims 255 and 271, Applicants note that none of the cited references teach or suggest a nucleic acid construct comprising a nucleotide sequence that encodes a gene product that is lethal to prokaryotes but not eukaryotes, where the nucleotide sequence further comprises a non-native intron that is excised from eukaryotes but not prokaryotes during processing. Since none of the cited references teach or suggest such a construct, the combination of references do not teach or suggest all of the claim elements and thus does not render those claims obvious.

With respect to claims 262 and 270, Applicants point out that none of the cited references teach or suggest a construct with a nucleotide sequence having a non-native intron inserted therein, where, when the intron is removed during processing, the gene product is expressed in a eukaryotic cell (but not a prokaryotic cell due to the presence of the intron) without any change in amino acid sequence from the native gene. As discussed under **IV.** above, Schwartz et al. only teach an intron where, upon removal, the gene product has additional amino acids compared to the native gene. See also the specification at paragraph **[0010]-[0011]** of US 2003/0104620, raising the point that the prior art had only inserted non-native introns using restriction sites, which unavoidably creates additional amino acid sequences. However, by using splice junctions, the Applicants could create precise splice sites with no additional amino acids in the product.

With regard to the point raised immediately above, and relevant to claims 262, 270 and 271, Applicants assert that Mount cannot properly be combined with Schwartz et al. and Deuschle et al., since there was no teaching or suggestion at the time of filing to utilize splice junctions rather than restriction sites to create non-native introns. Thus, in stating at p. 12 of the Office Action, "[a]lthough Schwartz is silent as to (C/A)AG sites, it would have been obvious and well within the technical grasp of a skilled artisan to insert the intron next to such a site given that these sequences were known in the art to be present at splice junction sites, which are crucial sites to the splicing of such intron sequences," the Office Action is engaging in hindsight assessment of the prior art, since there was no teaching or suggestion in the prior art at the time of filing of utilizing a splice junction rather than a restriction site in creating non-native introns. The Office Action appears to invoke *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. 398, 82 USPQ2d 1385 (2007) in stating that the substitution of splice junctions for restriction sites would be obvious even in the absence of any teaching or suggestion to do so, since *KSR* states that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 82 USPQ2d at 1395. See MPEP 2141.I. However, the substitution of restriction

sites with splice junctions is not a combination of familiar elements according to known methods, since splice junctions were not previously so manipulated in the prior art. Thus, Applicants use splice junctions in a novel way that was not previously set forth in the prior art. Therefore, the Office Action uses impermissible hindsight in asserting that the use of splice junctions instead of restriction sites is obvious. As such, the use of Mount in the cited combination of references is improper since there was no conception of the use of splice junctions for creation of non-native introns at the time of filling. In this light, it is clear that the claim element in claims 262, 270 and 271 stating "...said intron sequence is inserted within said sequence encoding said gene product and immediately 3' to (C/A)AG..." is a nonobvious element.

In view of the claim amendments and the above discussion, Applicants respectfully request withdrawal of the obviousness rejection under 35 U.S.C. 103(a).

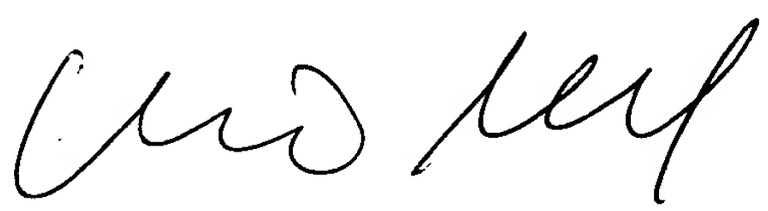
VI. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of rejections of record and examination of withdrawn claims 268 and 269, as those claims comprise all of the limitations of claims 245 and 262, respectively.

Applicants authorize the United States Patent and Trademark Office to charge all fees required to maintain pendency of this application, including the extension of time and Request for Continued Examination fees to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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